In re Application of: Itskovitz-Eldor et al
Serial No.: 10/536,734
Filed: May 27, 2005
Office Action Mailing Date: December 13, 2007

Examiner: Kim, Taeyoon
Group Art Unit: 1651
Attorney Docket: 29601

Amendments to the Drawings:

An attached sheet of annotated drawing includes an amendment to Figure 1a as required by the Examiner. In Figure 1a, "nesting" has been replaced by --nestin--. Figures 8-10 have been enhanced and are now visible.

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REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 193-234 are in this Application. Claims 194, 201 and 216-234 have been withdrawn from consideration. Claims 193, 195-200 and 202-215 have been rejected. Claims 203-204 and 206-213 have been canceled herewith. Claims 193, 196, 198 and 200 have been amended herewith.

Amendments To The Specification

The specification has been amended to remove the hyperlink code (HTTP://) from each of the three web sites referenced in the application.

Amendments To The Drawings

Corrected drawings sheets which comply with 37 CFR 1.121(d) are enclosed herewith.

Claim Objections

The Examiner objects to claim 210 for informalities that relate to language relating to the set of culturing conditions. Claim 210 has now been cancelled rendering moot any objection with respect to this claim.

35 U.S.C. § 112 Rejections

The Examiner has rejected claims 200, 210 and 211 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states that claim 200 discloses an Insulin secretion rate but does not discloses under which condition the rate is based on. Applicant has amended claim 200 to include the qualification that insulin secretion is measured under

conditions suitable for inducing insulin secretion from the cells. Description of such conditions are provided throughout the instant application (see pages 47-48).

Claims 210-211 has been cancelled herewith thereby rendering moot the Examiners rejection with respect to these claims.

The Examiner has also rejected claims 193, 195-200 and 202-215 under 35 U.S.C. § 112, First paragraph.

The Examiner states that the application describes various culturing conditions labeled as sets and that although the specification provides examples of such culturing conditions, it does not provide an adequate description for the entire scope of the claims.

In formulating this rejection the Examiner appears to have overlooked one important aspect of the invention, namely, that the invention is the sum of uniquely arranged steps and that each individual step or culturing condition utilized by the method of the invention is known to the ordinary skilled artisan.

Thus, mere mentioning of a step, or an outcome of a culturing step is sufficient to provide the ordinary skilled artisan withy the information necessary to carry out the step.

For example, one of ordinary skill in the art would be capable of selecting culturing conditions necessary for producing embryoid bodies containing cells displaying at least one characteristic associated with a pancreatic islet cell progenitor phenotype. Such conditions are described in the instant application and are further described in the prior art (see, for example, Lumelsky et al.). This holds true for all of the conditions described in the instant application, conditions for dissociating EBs, conditions for producing surface bound cell clusters including insulin producing cells etc.

The Examiner states that the description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made the invention. Applicant would like to point out that although the

claim limitations are defined by the results to be achieved, the specification provides the written description necessary to enable an ordinary skilled artisan to carry out the claimed method step. The instant application provides actual conditions (see the Examples section) for each step; however, since the conditions in themselves are not the subject matter of the invention, and are known to the ordinary skilled artisan the Examiners statement "that naming a type of material generally though to exists, in the absence of knowledge as to what the material consists of, is not a description of the entire material" is irrelevant to this case.

The present invention lies not in these conditions but rather in the unique sequence and selection of conditions. This ensures that the insulin-producing clusters or cell cultures (derived therefrom) of the present invention are substantially devoid of cells which cannot produce insulin or cannot mature into cells which produce insulin.

The purity of the cell/cluster culture produced by the present invention is clearly illustrated in the Examples section of the present invention. Although the Examiner contends that such purity (and insulin producing capability) is inherent to cultures produced by prior art methods (i.e. Lumelsky et al.), Applicant contends that this is simply not the case. Regardless of the results, the present methodology as claimed is clearly unique and different from that of Lumelsky et al. as is further argued below.

35 U.S.C. § 102 Rejections

The Examiner has rejected claims 193, 195 and 207-214 under 35 U.S.C. 102(a) as being anticipated by Lumelsky et al.

The Examiner states that Lumelsky et al. teach a method of producing pancreatic endocrine cells by generating embryoid bodies from mammalian ES cells in suspension culture and selecting nestin-positive pancreatic endocrine cells by culturing the cells of EBs on a substrate-coated surface. The pancreatic endocrine stem cells are then isolated and expanded and differentiated into mature endocrine cells which produce and secrete insulin.

Although Lumelsky et al. culture embryoid bodies and select for pancreatic endocrine cells, the actual methodology employed by Lumelsky et al. differs from that of the present invention in several important key steps.

Lumelsky et al. culture embryoid bodies or free stem cells under conditions which give rise to endocrine progenitors. Such conditions are used in order to induce the stem cells bound within EBs or free floating in suspension to differentiate into endocrine progenitors. Following such initial differentiation, Lumelsky et al. isolate differentiated stem cells by selecting nestin-positive cells which adhere to coated plates. Following selection and isolation of such cells, they are expanded in culture and differentiated into mature insulin producing cells.

Section 0098 of US 2004/0121460 clearly set forth the conditions used by Lumelsky et al.:

"The cells of the embryoid body are cultured to select for pancreatic endocrine stem cells or pancreatic endocrine cell precursors. In one embodiment, to select for pancreatic endocrine stem cells or precursor cells, the EB cells are plated onto a surface that permits adhesion of pancreatic endocrine stem cells or precursor cells, for example a fibronectin-, laminin-, or vitronectin-coated surface. In another embodiment, embryoid bodies are not generated, but ES cells are directly plated onto the surface." (emphasis added)

The present methodology differs from that of Lumelsky in that it includes a method step which substantially increases the homogeneity of the resultant culture prior to expansion.

Although the present methodology employs initial steps that are similar in nature to those described by Lumelsky et al., i.e. generation of EBs and isolation of progenitors, the present methodology employs an additional purification step which substantially enhances the homogeneity and the insulin–producing capabilities of the resultant culture.

Following isolation of the progenitors from EBs, the present method employs an addition cell selection step which leads to formation of surface bound clusters. Such a step serves two purposes, it concentrates the endocrine progenitors into readily

harvestable surface-bound clusters and it ensures that the clusters are substantially free of non-endocrine cells, since such cells cannot adhere to the substrate.

Such a step is missing from the teachings of Lumelsky et al. as is any suggestion that further purification of the culture is necessary or desired since simply put, the nestin selection step employed thereby is regarded as sufficient.

Although Lumelsky et al. describe generation of islets, such generation is not effected using precursor cells but rather expanded endocrine cells which naturally aggregate into clusters in suspension cultures. Thus, the islets of Lumelsky et al. would not have purity and insulin producing capability of the clusters of the present invention (or any islets formed therefrom) since they would inherently include a larger proportion of non-insulin producing cells.

Example 1 of the instant application clearly set forth the advantages of using the additional purification step of the present method:

"Stage VI – generation of isolated, highly differentiated, high-level insulin producing suspended islet like cell clusters having long term in-vitro longevity: Surface bound islet like cell clusters from Stage V culture were dissociated by trypsin-EDTA treatment and cultured for up to 2 weeks under non adherent "suspension" conditions in uncoated plastic Petri dishes (Ein-Shemer) in Medium 3. This step resulted in prolongation of islet like cell cluster survival beyond 2 weeks, a sharp increase in insulin secretion, and a reduction in the proportion of neuronal and mesenchymal cells in the cell clusters. The use of such suspension culturing conditions has been previously demonstrated to prolong the longevity of insulin secreting human islets derived from adult donor derived cells (Zhao M. et al., 2002. Transplantation 73:1454–1460).

Clearly, a culture resultant from the culturing conditions employed by the present invention provides numerous benefits including prolonged survival and increased insulin production.

Thus, Applicant is of the opinion that the invention embodied by now amended claim 193 and claims dependent therefrom is neither anticipated nor rendered obvious by the teachings of Lumelsky et al.

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35 U.S.C. § 103 Rejections

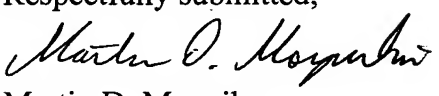
The Examiner has rejected claims 193, 195-200 and 202-215 under U.S.C. 103(a) as being unpatentable over Lumelsky et al. in view of Ling et al.

The Examiner has further rejected claim 205 under U.S.C. 103(a) as being unpatentable over Lumelsky et al. in view of Thomson et al.

The differences between Lumelsky et al. and the presently claimed invention are discussed above. Ling et al. or Thomson et al. do not add teachings which pertain to the additional purification step of the present invention, nor do they or Lumelsky et al. provide one of ordinary skill in the art with motivation or reason to include such step. Thus, the combination of Lumelsky et al. and Ling et al. or Thomson et al. or any other prior art reference does not render obvious the present invention as now claimed.

In view of the above amendments and remarks it is respectfully submitted that claims 193, 195-200, 202-205 and 214-215 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



Martin D. Moynihan
Registration No. 40,338

Encls:

- Letter to Chief Draftsman
- Annotated Drawing
- Formal Drawing Transmittal Letter
- Replacement Sheets
- Petition for Color Drawings
- Three (3) Sets of Color Drawings